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Similar relative risks of seizures following measles containing vaccination in children born preterm compared to full-term without previous seizures or seizure-related disorders

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Abstract

Background: Febrile seizures are associated with the first dose of measles-containing vaccines and the risk increases with chronologic age during the second year of life. We used the Vaccine Safety Datalink (VSD) to determine if the relative increase in risk of seizures following receipt of measles-containing vaccine differs by gestational age at birth.

Methods: Children were eligible if they received their first dose of measles-containing vaccine at age 12 through 23 months from January 2003 through September 2015. Children were excluded if they had a history of seizure or conditions strongly related to seizure prior to 12 months of age. Seizures were identified by diagnostic codes in the inpatient or emergency department settings. Using risk-interval analysis, we estimated the incidence rate ratio (IRR) for seizures in the 7 through 10 days (risk period) vs 15 through 42 days (control period) following receipt of measles-

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Conflicts of interest

The remaining authors report no conflicts of interest.

containing vaccines in children born preterm (<37 weeks gestation age) and those born full-term (≤37 weeks).

Results: There were 532,375 children (45,343 preterm and 487,032 full-term) who received their first dose of measles-containing vaccine at age 12 through 23 months. The IRRs of febrile seizures 7 through 10 days compared with 15 through 42 days after receipt of measles-containing vaccine were 3.9 (95% CI: 2.5–6.0) in preterm children and 3.2 (2.7–3.7) in full-term children; the ratio of IRRs: was 1.2 (0.76–1.9), p = 0.41. IRRs were also similar across gestational age groups, by vaccine type received (measles-mumps-rubella [MMR] or measles-mumps-rubella-varicella [MMRV]) and age at vaccination (12–15 or 16–23 months).

Conclusion: Vaccination with a measles-containing vaccine in the second year of life is associated with a similar relative risk of a first seizure in children born preterm as in those who were born full-term.

Keywords

Measles containing vaccine; MMR; MMRV; Seizures; Preterm; Premature

1. Background

Combination measles-mumps-rubella (MMR) and measles-mumps-rubella-varicella (MMRV) vaccines are two measles-containing vaccines currently available in the United States [1]. Measles-containing vaccines are associated with an increased risk of febrile seizures in the second week after vaccination [2–8]. Among children aged 12 through 23 months, the risk of febrile seizures is approximately 2 times higher in those who received the first dose as MMRV vaccine compared to those who received separate MMR and varicella vaccines at the same visit [5,9]. Age at vaccination has also been associated with risk of seizures. Children who received their first dose of measles-containing vaccine at age 16–23 months had a higher risk of seizures than those vaccinated at age 12–15 months, the age recommended by the U.S. Advisory Committee on Immunization Practices (ACIP) [1,6,10]. Although the biological mechanism for febrile seizures is unclear, the age associated risk is likely due to multiple factors, including peak incidence of febrile seizures occurring at age 15–18 months [11] and maturation of the brain's sensitivity to fever [12]. Additionally, differences in the underlying medical conditions or health-seeking behaviors may exist between those who are vaccinated at the recommended age versus those who receive it later [6]. Parents of preterm infants may delay MMR vaccination for their child [13,14], as the incidence of febrile seizures is higher in children who are born preterm than those born full-term [15–17]. However, data concerning the safety of vaccination in children born preterm compared to children born full-term is limited particularly for vaccinations received during the second year of life [18,19].

We aimed to examine if the risk of febrile seizures during the 7 through 10 days versus 15 through 42 days following receipt of measles-containing vaccine is increased in children born preterm compared to children born full-term. We also assessed whether the difference in risk of febrile seizures following receipt of measles-containing vaccine (if any) might vary

by vaccine type received (MMR or MMRV) or age at vaccination (12 through 15 or 16 through 23 months).

2. Methods

2.1. Study population

The study population consisted of children who received their first dose of measles-containing vaccine at age 12 through 23 months from January 1, 2003 through September 30, 2015. These children were members at seven integrated health care organizations (sites) located throughout the United States that participate in the Centers for Disease Control and Prevention (CDC) sponsored Vaccine Safety Datalink (VSD) [20,21]. Institutional Review Boards at each VSD site approved this study with a waiver of informed consent.

Children were included if they were born at a study site facility, were continuously enrolled as members of the study site to age 24 months, and had gestational age data. Estimated gestational age at birth was determined from the VSD pregnancy algorithm [22]. In brief, the algorithm captures gestational age from each site's electronic medical record databases (e.g., procedure dates, ultrasound reports, laboratory tests and dates) and supplemented with birth certificate data from the corresponding state vital records office. When gestational age was not available, it was imputed using published outcome specific averages or definitions. [22]. We classified children born before 37 weeks gestational age as preterm and children born 37 weeks gestational age as full term [23]. We also further classified preterm into those born <35 weeks (early preterm) and 35 through 36 weeks (late preterm) gestational age. Children with epilepsy, cerebral palsy, severe head trauma, intraventricular hemorrhage, intracranial tumor, meningitis, or encephalitis based on documented *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnostic codes in the electronic medical record were excluded (Supplemental Table). Children with an ICD-9-CM coded diagnosis of seizure prior to 12 months of age were also excluded. The exclusion criteria were determined by consensus of coauthors and were conditions known to be associated with increased risk of seizures or recurrence of seizures.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.11.038.

2.2. Outcome

A seizure was defined as the first emergency department or inpatient hospital encounter with ICD-9-CM diagnostic code of 780.3 (convulsions) during the 42-days following vaccination; we did not distinguish between febrile and afebrile seizures. However, previous VSD studies have found a high confirmation rate (94% for acute seizures, 87% for acute febrile seizures) for this diagnostic code when assigned from emergency department or inpatient hospital encounters [5,6,16,24].

2.3. Analytic approach

We conducted a risk-interval analysis among vaccinated children [25] with each child having 42 days of follow-up following receipt of a measles-containing vaccine. Days 7 through 10

following vaccination were defined as the risk interval and days 15 through 42 following vaccination were defined as the control interval. Days 0 through 6 and 11 through 14 following vaccination were excluded. The first exclusion reduced possible short-term effects with concomitant vaccines [3,26–28] and the latter exclusion was to avoid residual exposure effects in the control interval. Children with seizures occurring in these excluded intervals were excluded in the analysis.

Seizure incidence rates and 95% confidence intervals per 1000 person-years were calculated for the risk and control intervals. To examine the possible effect of gestational age differences, we compared the incidence rate ratios (IRRs) of seizures between children born preterm and those born full-term using a Poisson regression model with an effect-modification term for gestational age category by exposure status (risk or control interval). The effect modification estimate was expressed as the ratio of IRRs with its 95% confidence interval and p-value [29]. Separate models were generated by vaccine received (MMR and MMRV) and by child's age at vaccination (12 through 15 and 16 through 23 months) since seizure risk following vaccination differ by vaccine type and age at vaccination, respectively [5–7].

We also performed a temporal scan of all cases within 1 through 42 days post vaccination interval [30] to determine if the 7 through 10 day risk interval was appropriate for the gestational age categories, vaccine received, and child's age at vaccination. Periods in the 1 through 42 days post vaccination among the largest log-likelihood were considered clusters for further analysis.

All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

3. Results

There were 556,864 children who received their first dose of measles-containing vaccine at age 12 through 23 months. Of these, 24,489 children were excluded because of documented history of seizure before age 12 months (<1%) or other exclusionary diagnoses (4%). The remaining 532,375 children were included in the analysis; 45,343 were born preterm (8.5%) and 487,032 born full-term (91.5%). There were no meaningful differences between those born preterm and full-term by sex, age at vaccination, or maternal age (Table 1). As expected, children born preterm had lower mean birth weights (30% less) than those born full-term.

Of the 996 children with a seizure episode during the 42 days following vaccination, 167 seizures occurred 0 through 6 or 11 through 14 days after vaccination and were excluded. The remaining 829 children with seizures were included in the analysis; 87 in children born preterm (32 in children born <35 weeks gestational age and 55 in children born 35 through 36 weeks) and 742 in those born full-term. Seizures occurred in the 7 through 10 days post-vaccination risk period in 263 children and in the 15 through 42 days post-vaccination control period in 566 children. The mean age at seizure events were similar for both children born preterm (13.5 months) and children born full-term (13.3 months).

In the overall primary analysis, the IRR point estimate of children born preterm was 20% larger than children born full-term, although the precision was low [ratio of IRRs: 1.2 (0.76–1.9), p = 0.41], (Table 2). From the secondary analyses, similar IRR results were observed for children born <35 weeks or 35 through 36 weeks gestational age, among those receiving MMR or MMRV, and children vaccinated at age 12 through 15 months. For children vaccinated at age 16 through 23 months, the point estimate IRR was 20% lower for children born preterm vs full-term; precision was also low [ratio of IRRs: 0.82 (0.20–3.4), p = 0.79]. Overall, and for all vaccine and age strata, the risk-interval (exposed) incidence rates were 20–40% larger for children born preterm vs. full-term. The largest incidence rate point estimate was for children born preterm who received MMRV (100 seizures per 1000 person-years). The lowest point estimate (10 seizures per 1000 person-years) was observed for full-term children vaccinated at age 16 through 23 months during the unexposed control interval.

Temporal scans showed that the 7 through 10 day post-vaccination period was identified as a high-risk cluster overall and in the gestational age and vaccine type subgroups (Supplemental Figures).

4. Discussion

We examined the incidence rates and incidence rate ratios of seizures following receipt of measles-containing vaccine in the second year of life by gestational age for children without previous seizures or seizure-related disorders. Generally, the exposed incidence rate and IRR point estimates were similar among children born pre-term compared to full-term. The ratio of IRRs in the two groups were near 1, with 95% confidence intervals that ranged from <1 to substantially >1. Infants born preterm are recommended to receive vaccinations at the same chronological age recommended for infants born full-term [31]. Existing data for vaccination of preterm infants are reassuring with no apparent safety concerns, and although immune response to vaccines in the first year of life may be lower for infants born preterm than full-term, the differences are likely to be not clinically relevant [32]. For vaccinations received during the second year of life, differences in immune response between preterm and full-term are less significant [33]. In our study, the overall incidence rate of seizures following vaccination was low and the incidence rate ratios essentially did not differ between children born preterm and those born full-term. The increased risk with delayed receipt of measles-containing vaccine or with receipt of MMRV is consistent with previous VSD studies [5–7], and is unrelated to gestational age.

This was a large population based study with highly accurate vaccination dates [34] and use of previously validated diagnostic codes for the seizure outcome [5,6,16,24]. However, our study had several potential limitations. First, we did not include children who may have delayed receipt of measles-containing vaccine past age 23 months. Second, there were relatively few seizure cases among children born preterm, particularly among those who were vaccinated after age 15 months and those who received MMRV vaccine. Third, most of the preterm children were born at 35 through 36 weeks gestational age (late preterm) while few children were born at <35 weeks gestational age. Finally, we excluded children with a previous history of seizure or risk factors related to seizure so our results may not apply to this population. Notably, “personal or family history of seizures” is a precaution (but not a

contraindication) of measles-containing vaccines [1]. We excluded children with a personal history of seizures before 12 months of age, based on electronic diagnostic codes, in our attempt to independently assess the risk of seizures due to measles-containing vaccines among children born preterm. We were not able to assess family history, as data were not readily available in the electronic health record.

In conclusion, our results support the current ACIP recommendations to administer the first dose of measles-containing vaccine at age 12 through 15 months for all children, including those born preterm [1,13,31]. Delaying vaccination of measles-containing vaccines may increase the risk of seizures following vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of children aged 12–23 months at the time of receipt of first dose of measles-containing vaccine by gestational age.

	Gestational age category (weeks)	
	Preterm (<37)	**Full-term (≤37)**
Number of children	45,343	487,032
Vaccine received, n (%)		
MMR	37,262 (82.2)	403,238 (82.8)
MMRV	8081 (17.8)	83,794 (17.2)
Sex, n (%)		
Female	20,779 (45.8)	239,775 (49.2)
Male	24,564 (54.2)	247,257 (50.8)
Age at vaccination in months, mean (SD)	13.30 (1.98)	13.33 (2.01)
Calendar month of vaccination, n (%)		
November through April	22,197 (49.0)	234,430 (48.1)
May through October	23,146 (51.0)	252,602 (51.9)
Birth weight in grams, mean (SD)	2417 (6 4 9)	3449 (4 7 4)
Maternal age in years, mean (SD)	31.9 (5.7)	31.1 (5.3)

Abbreviations: MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; SD, standard deviation.

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Table 2

Incidence rate (per 1000 person-years) and rate ratios of seizures following vaccination overall and by gestational age category, child's age at vaccination, and vaccine received.

		7 through 10 days after vaccination (risk interval)		15 through 42 days after vaccination (control interval)			
Gestational age category	**Number of children**	**Number of seizures**	**Incidence rate[a] (95% CI)**	**Number of seizures**	**Incidence rate[a] (95% CI)**	**IRR (95% CI)[b]**	**Preterm vs full-term, ratio of IRR (95% CI), p**
Overall							
Preterm (<37 weeks)	45,343	31	62 (42–89)	56	16 (12–21)	3.9 (2.5–6.0)	1.2 (0.76–1.9), 0.41
<35 weeks	16,586	10	55 (26–100)	22	17 (11–26)	3.2 (1.5–6.7)	1.0 (0.47–2.1), 0.99
35–36 weeks	28,757	21	67 (41–100)	34	15 (11–22)	4.3 (2.5–7.4)	1.4 (0.77–2.4), 0.29
Full-term (≥37 weeks)	487,032	232	43 (38–49)	510	14 (12–15)	3.2 (2.7–3.7)	
Vaccine received							
MMR							
Preterm	37,262	22	54 (34–82)	48	17 (12–22)	3.2 (1.9–5.3)	1.2 (0.70–2.0), 0.51
Full-term	403,238	163	37 (31–43)	425	14 (12–15)	2.7 (2.2–3.2)	
MMRV							
Preterm	8081	9	100 (47–190)	8	13 (5.6–25)	7.9 (3.0–20)	1.4 (0.51–3.8), 0.52
Full-term	83,794	69	76 (59–95)	85	13 (11–16)	5.7 (4.1–7.8)	
Child's age at vaccination							
12–15 months							
Preterm	41,391	27	60 (39–87)	51	16 (12–21)	3.7 (2.3–5.9)	1.3 (0.77–2.1), 0.36
Full-term	442,919	200	41 (36–47)	477	14 (13–15)	2.9 (2.5–3.5)	
16–23 months							
Preterm	3952	4	92 (25–237)	5	17 (5.4–39)	5.6 (1.5–21)	0.82 (0.20–3.4), 0.79
Full-term	44,113	32	66 (45–94)	33	10 (6.7–14)	6.8 (4.2–11)	

Abbreviations: MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; IRR: incident rate ratio, CI, confidence interval.

[a] Per 1000 person-years.

[b] IRR (7–10 days versus 15–42 days after vaccination).